UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,925	09/24/2003	William Hildebrand	66802.055	4622

30589 7590 05/15/2009

DUNLAP CODDING, P.C.
PO BOX 16370
OKLAHOMA CITY, OK 73113

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	
MAIL DATE	**DELIVERY MODE**
05/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,925	HILDEBRAND ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42,45,46,48-51,60 and 61* is/are pending in the application.

4a) Of the above claim(s) *38-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-37, 42, 45, 46, 48-51, 60, 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed 1/22/09 is acknowledged and has been entered.

The Declaration of Inventor Rico Buchli under 37 C.F.R. 1.132 filed 1/22/09 is acknowledged and has been entered.

The Declaration of Inventor William H. Hildebrand under 37 C.F.R. 1.132 filed 1/22/09 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I and species of ELISA plate as the substrate, antibody as the anchoring moiety, W6/32 as the antibody, as well as Applicant's election of the species of HLA-A2 with traverse in Applicant's amendment and response filed 12/1/06.

Claims 31-37, 42, 45, 46, 48-51, 60 and 61 are currently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 31-37, 42, 45-51, 60 and 61 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the disclosure as originally filed is as follows: "at least one MHC trimolecular complex linked thereto" recited in instant base claim 31, "at least one MHC trimolecular complex" recited in claims 35 and in claim 61.

Applicant's arguments have been fully considered, but are not persuasive. Applicant's said arguments are of record on pages 8-9 of the amendment filed 1/22/09. Applicant points to support for the amendatory material at paragraph [0087] of the instant application and paragraph [0002] of parent application serial no. 10/022,066.

Although Applicant has support for an MHC trimolecular complex, base claim 31 is drawn to a method wherein a single individual MHC heavy chain allele is amplified in a locus-specific manner to produce a PCR product that encodes one particular or individual soluble MHC class I heavy chain, transfecting a mammalian cell line that expressed endogenous (cell bound) MHC molecules, culturing the transfected cell line, and collecting and purifying the one or individual soluble MHC allele product away from other proteins; yet a subsequent method step recites "linking at least one soluble MHC trimolecular complex to a substrate." Hence the claim encompasses linking more than one soluble MHC trimolecular complex to a substrate, *i.e.,* meaning either that the "at least one soluble MHC trimolecular complex" encompasses more than one MHC heavy chain allele product (for example, HLA-A2 and HLA-B8) or that it encompasses linking one molecule of the particular one MHC heavy chain allele product to the substrate (for example, one molecule of HLA-A2 soluble heavy chain).

5. Claims 31-37, 42, 45, 46, 48-51, 60 and 61 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material (in the prior amendment filed 8/20/07) not supported by the disclosure as originally filed is as follows: "wherein the mRNA encodes at least one MHC heavy chain allele" recited in claim 31.

Applicant's arguments have been fully considered, but are not persuasive. Applicant's said arguments are of record on pages 9-10 of the amendment filed 1/22/09. Applicant points to support for the amendatory material at paragraphs [0013], [0015], [0023], [0066] and figures 1 and 2 and their corresponding legends/detailed descriptions.

However, as Applicant points out, the disclosure at [0015] is "HLA allele mRNA from a source is isolated and reverse transcribed to obtain allelic cDNA", meaning mRNA from a "source" not "mRNA encodes at least one MHC heavy chain allele." "Source" does not specify how many mRNAs there are that encode an MHC heavy chain allele, and "at least one MHC heavy chain allele" has no upper boundary as to the number of alleles. The Examiner notes that in paragraph [0056] not cited by Applicant, the disclosure is to obtaining gDNA or cDNA that encodes the desired MHC molecule, and alleles at the locus that encode the desired MHC molecule are PCR amplified in a locus specific manner. Such disclosure is not equivalent to "mRNA encodes at least one MHC heavy chain allele", and "isolating mRNA from a source" also recited in the base claim 31. In addition, [0018] discloses that when HLA allele mRNA is used, the source is selected from the group consisting of mammalian DNA and an immortalized cell line. When gDNA which encodes an HLA allele is used, the gDNA is obtained from blood, saliva, hair semen, or sweat. Thus the disclosure indicates that the number of HLA alleles

from these sources is limited and does not include an open upper limit as is encompassed by the recitation of "mRNA encodes at least one MHC heavy chain allele".

6. Applicant is reminded that for the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application, *i.e.,* 9/24/03, as the parent applications do not support the claimed limitations of the instant application. The provisional parent application serial no. 60/413,842 only discloses ELISA assays using W6/32 or pan-HLA antibody immobilized HLA to detect anti-HLA antibodies. The provision parent application serial no. 60/474,655 discloses some aspects of making soluble HLA from gDNA or cDNA. The parent application serial no. 10/337,161 and 10/022,066 disclose soluble HLA and making soluble HLA, respectively. In addition, the provisional parent applications do not disclose "pool" and "at least one MHC trimolecular complex" in the context of the claimed method.

7. With regard to Applicant's arguments in response to the 35 USC 103(a) rejections of record in the prior Office Action and in response to the Declarations of Inventors Rico Buchli and William H. Hildebrand under 37 CFR 1.132, both filed 1/22/09, the Examiner points out that prior to elution from BBM.1-S4b, or W6/32, the HLA complexes were not denatured. However, in light of the recitation of the limitation "soluble" in the instant claims, the Examiner has reconsidered her position. The following rejections are hereby withdrawn:

The prior rejection of record of claims 31-37, 42, 45, 46, 48-51, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,482, 841 (IDS reference) in view of U.S. Patent No. 5,292,641 (IDS reference), Prilliman *et al* (Immunogenetics. 1997, 45: 379-385, IDS reference), DiBrino *et al* (Biochemistry. 1995, 34(32): 10130-10138, of record) and Zemmour *et al* (J. Immunol. 1992, 148(6): 1941-1948).

The prior rejection of record of claims 31-37, 42, 45, 46, 48-51, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,482, 841 (IDS reference) in view of U.S. Patent No. 5,292,641 (IDS reference), US 2002/0197672 A1, Prilliman *et al* (Immunogenetics. 1997, 45: 379-385, IDS reference) and DiBrino *et al* (Biochemistry. 1995, 34(32): 10130-10138, of record).

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 31-37, 42, 45, 46, 48-51, 60 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,482, 841 (IDS reference) in view of U.S. Patent No. 5,292,641 (IDS reference), U.S. Patent No. 6,232,445 (IDS reference), DiBrino *et al* (Biochemistry. 1995, 34(32): 10130-10138, of record) and Zemmour *et al* (J. Immunol. 1992, 148(6): 1941-1948, of record) and by an admission in the specification at page 42 and Figure 7.

U.S. Patent No. 5,482, 841 discloses an assay method for detecting the presence of anti-HLA antibodies in a sample, said assay comprising HLA molecules extracted from cells and purified by detergent extraction, centrifugation, PEG and NH_4SO_4 precipitation, said HLA molecules indirectly linked to a solid support such as beads, membranes and microtiter plates by polyclonal or monoclonal antibodies specific for the α3 domain of Class I HLA or the associated β2m chain or to a conformational epitope expressed by the combination of both chains, or specific to epitopes conserved across a class or subset of HLA molecules, such as ones specific for HLA-A, B or C. U.S. Patent No. 5,482, 841 further discloses that a sample containing antibodies is added, bound antibodies are separated from free antibodies and other non-specifically bound proteins or other components, and the presence of the antibodies is detected using a labeled reagent such as anti-human antibody against IgG, IgM or IgA. U.S. Patent No. 5,482, 841 discloses that the samples may be biological fluids such as blood, CSF, tears, saliva, lymph, dialysis fluid, organ or tissue culture derived fluids and fluids extracted from physiological tissues. U.S. Patent No. 5,482, 841 discloses that of particular interest are allo-antibodies found in the serum of transplant or prospective transplant patients, and that the determination of the presence and specificity of antibodies against foreign HLA antigens is therefore clinically important for monitoring transplant patients, and the assay may test for reactivity against a panel of antigens or may be specific for a single donor. U.S. Patent No. 5,482, 841 discloses that the solid support can be microtiter plates (with wells), glass, plastic, polysaccharides, nylon or nitrocellulose [membranes] or paramagnetic component materials surrounded by plastic. U.S. Patent No. 5,482, 841 discloses using negative and positive control samples. U.S. Patent No. 5,482, 841 discloses a kit for use in a method for detecting at least one receptor analyte specific for an HLA antigen in a biological sample, said kit comprising a solid support coated with a capture agent capable of specifically binding to a conserved region of a subset of interest of HLA antigens and a labeled reagent that specifically binds to human antibodies, and wherein the capture agent may be an antibody directed to the 3 domain of HLA class I heavy chain (see entire reference).

U.S. Patent No. 5,482, 841 does not disclose wherein the pool of HLA molecules is recombinantly produced as recited in the instant claims.

U.S. Patent No. 5,292,641 discloses a kit that includes HLA antigens bound to a solid support, control solutions, and the reagents necessary for the determination of antibodies specific for the HLA antigens (especially column 5 at lines 35-49). U.S. Patent No. 5,292,641 discloses an assay method that utilizes HLA bound to a solid support, said HLA being Class I or Class II or minor histocompatibility antigens and derived from human donors, including from platelets, plasma, serum, lymphoblastoid cell lines, transfectant cell lines, or any other convenient source, said solid support including microtiter plate wells, test tubes, beads, slides, absorbent films, membranes, particles, magnetic particles, glass or plastics. U.S. Patent No. 5,292,641 discloses ELISA techniques and the use of labeled anti-human bodies for detection (see entire reference).

U.S. Patent No. 6,232,445 discloses large-scale production of large quantities of an individual, functional, soluble MHC molecule, including an MHC class I HLA molecule. US 6,232,445 discloses isolation of total mRNA from total mRNA from an immortalized cell line source, reverse transcribing mRNA to form cDNA, PCR amplification of MHC molecules truncated to exclude the transmembrane and cytoplasmic domains (*i.e.,* including a stop codon and thus making it soluble), cloning the PCR product into a mammalian expression vector comprising a promoter, and that the soluble MHC molecule may comprise a tail or tag such as 6x-His that can be used for purification, or alternatively, an anti-HLA antibody specific for a conformational epitope may be used for immunoaffinity purification of properly folded HLA molecules, including an elution from the anti-HLA antibody at pH 11 that leaves the complex intact. US 6,232,445 discloses transfection the mammalian expression vector into a variety of cell types including the mammalian cell line HeLa that is a human ovarian cancer cell line (that has endogenous peptides that can load into the antigen binding groove of the HLA class I molecule) and inoculating hollow fiber bioreactors for large scale continuous production of soluble individual and functional individual MHC class I molecules. While the examples recited in U.S. Patent No. 6,232,445 used MHC class II molecules for exemplification of the method, U.S. Patent No. 6,232,445 discloses that both MHC class II and class I molecules are embraced by the practice of the method. Furthermore, it is well within the purview of the artisan to obtain primers for practicing the method of U.S. Patent No. 6,232,445 and use them to amplify the extracellular domains of MHC class I in the same manner as the MHC class II molecules exemplified (see entire reference, especially column 25 at lines 42-65, column 27 at lines 7-26, column 28 at lines 49-67, column 29 at lines 34-67, column 31 at lines 48-54, column 47 at lines 31-54, claim 7, column 48 at lines 55-67, column 49 at lines 1-3, column 54 at lines 45-67, column 58 at lines 1-14, column 2 at lines 50-67, column 3 at lines 1-47, figure 5B).

DiBrino *et al* teach obtaining and full length cDNA for HLA-B*4403 by PCR amplification of cDNA made from RNA isolated from the immortalized human lymphoblastoid B cell line W1B. The cDNA was sequenced, cloned into the expression vector RSV.neo and transfected into Hmy2.C1R cells (class I deficient cell line). DiBrino *et al* teach detection of said HLA using W6/32 monoclonal antibody specific for human Class I molecules. DiBrino *et al* teach HLA-A2 class I HLA molecules (especially materials and methods section).

Zemmour *et al* teach that Hmy2.C1R cells express HLA-Cw4 as well as reduced levels of HLA-B35 (especially abstract).

The admission in the specification at page 42 and Figure 7 is that soluble HLA retains its structure and bound peptide when eluted with pH 11.0 buffer.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have provided recombinantly produced HLA molecules and to have used them in the method for determining anti-HLA antibodies disclosed by U.S. Patent No. 5,482, 841 and U.S. Patent No. 5,292,641. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to disclosed by U.S. Patent No. 6,232,445 using any suitable mammalian cell lines such as the HeLa cell line disclosed by U.S. Patent No. 6,232,445 or the Hmy2.C1R cell line taught by DiBrino *et al* and by Zemmour *et al*, and including the use of W6/32 antibody as a capture agent, and to have included a step of obtaining cDNA encoding class I by reverse transcribing RNA isolated from an immortalized human cell line as taught by DiBrino *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a more easily produced and easily purified source of soluble HLA molecules for use in the method for detecting the presence of anti-HLA antibodies in a sample.

With regard to the limitation “wherein the mammalian cell line expresses endogenous MHC molecules" recited in base claim 31, two references cited in the instant rejection teach the cell line Hmy2.C1R that does express endogenous MHC molecules, and thus the art meets the said claim limitation.

Applicant’s arguments have been fully considered, but are not persuasive.

Applicant’s arguments are of record in the amendment filed 1/22/09 on pages 11-16.

The Examiner points out that this rejection is a new ground of rejection. The Examiner will address Applicant’s arguments that pertain to the instant rejection.

Applicant argues that the fact that the Examiner had to combine teachings from five different references demonstrates that a case of prima facie obviousness has not been established and that hindsight has been used.

In response to Applicant's argument that the Examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir.1991).

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant is arguing the remainder of the references separately.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.1986).

With regard to Applicant's arguments concerning the class I deficient cell line taught by DiBrino *et al* and by Zemmour *et al*, the instant claim 31 recites that the cell line "expresses multiple surface-bound native Class I endogenous MHC molecules". Thus, the art references meet the claim limitations as the Hmy2.C1R cell line expresses HLA-Cw4 as well as reduced levels of HLA-B35.

Applicant argues that Zemmour *et al* teach a cell line that is negative for native HLA-A, B expression, that HLA-C proteins is a fraction of the expression of HLA-A, B molecules and the HLA-B35 allele is a novel, non-native subtype and is produced at greatly reduced levels that are not even detectable by antibodies or complement.

However, with regard to the reduced levels of HLA-C and HLA-B, claim 31 recites that the cell line expresses multiple surface-bound native class I endogenous MHC molecules. The HLA-C molecules are multiple, are surface-bound and are native class I endogenous MHC molecules for the Hmy2.C1R cell line. With regard to the HLA-B35 allele, Applicant cites the abstract, page 1941 at column 1, lines 19-32 in support of the allegation that HLA-B35 is a non-native subtype. However, although the HLA-B35 allele expressed in the Hmy2.C1R cell line is a point mutation of the HLA-B35 allele in one of the cell lines from which the Hmy2.C1R cell line was derived, none-the-less, the point mutation allele is an endogenous or native MHC molecule for the Hmy2.C1R cell line.

With regard to Applicant's argument about the HLA-B35 molecule not being detectable with antibodies or complement, the HLA-B35 molecule is detectable by CTL, thus indicating that they are multiple and cell surface bound class I molecules. The art meets the claim limitations.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
May 4, 2009

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644